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Authors

Ikeda, Sadakatsu
Elkin, Sheryl K
Tomson, Brett N
et al.

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RESEARCH PAPER



Next-generation sequencing of prostate cancer: genomic and pathway alterations, potential actionability patterns, and relative rate of use of clinical-grade testing

Sadakatsu Ikeda^{a,b}, Sheryl K. Elkin^c, Brett N. Tomson^c, Jennifer L. Carter^c, and Razelle Kurzrock^a

^aCenter for Personalized Cancer Therapy, Division of Hematology/Oncology, Department of Medicine, University of California, San Diego, Moores Cancer Center, La Jolla, CA, USA; ^bCancer Center, Tokyo Medical and Dental University, Tokyo, Japan; ^cN-of-One, Inc, Lexington, MA, USA

ABSTRACT

Despite being one of the most common cancers, treatment options for prostate cancer are limited. Novel approaches for advanced disease are needed. We evaluated the relative rate of use of clinical-grade next generation sequencing (NGS) in prostate cancer, as well as genomic alterations identified and their potential actionability. Of 4864 patients from multiple institutions for whom NGS was ordered by physicians, only 67 (1.4%) had prostate cancer, representing 1/10 the ordering rate for lung cancer. Prostate cancers harbored 148 unique alterations affecting 63 distinct genes. No two patients had an identical molecular portfolio. The median number of characterized genomic alterations per patient was 3 (range, 1 to 9). Fifty-six of 67 patients (84%) had ≥ 1 potentially actionable alteration. *TP53* (55.2% of patients), *PTEN* (29.9%), *MYC* (17.9%), *PIK3CA* (13.4%), *APC* (9.0%), *BRCA2* (9.0%), *CCND1* (9.0%), and *RB1* genes (9.0%). The PI3K (52.2% of patients), WNT (13.5%), DNA repair (17.9%), cell cycle (19.4%), and MAPK (14.9%) machinery were commonly impacted. A minority of patients harbored *BRAF*, *NTRK*, *ERBB2*, or mismatch repair gene abnormalities, which are highly druggable in some cancers. Only ~ 10% of prostate cancer trials (clinicaltrials.gov, year 2017) applied a (non-hormone) biomarker before intervention. In conclusion, though use of clinical-grade NGS is relatively low and only a minority of trials deploy DNA-based biomarkers, many prostate cancer-associated molecular alterations may be pharmacologically tractable with genomically targeted therapy or, in the case of mismatch repair anomalies, with checkpoint inhibitor immunotherapy.

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prostate cancer; genomic profiling; next-generation sequencing; molecular targeted therapy; mutation

Introduction

Prostate cancer is the most common cancer and a leading cause of death in American men.¹ Hormone therapy has been the cornerstone of treatment for decades.² Molecular targeted therapy has been changing the treatment landscape in other malignancies, such as non-small cell lung, breast, and colorectal cancer. However, no genomically targeted therapy is approved by the Food and Drug Administration (FDA) for prostate cancer, and, historically (September 2011 through September 2014), only ~ 2.0% of prostate cancer clinical trials listed on clinicaltrials.gov utilized a non-hormone biomarker to match patients with therapy.²

Genomic profiling of cancer using next-generation sequencing (NGS) is gaining popularity in the clinical setting.^{3–8} By sequencing the tumor genome, potential actionable genomic aberrations can be discovered. Mutation profile can be used as a biomarker to guide appropriate matched targeted therapy and is also emerging as a marker for immunotherapy, with specific alterations such as *PDL1* amplification, aberrant mismatch repair genes and high tumor burden being correlated with responsiveness.⁹

In order to better understand the landscape of prostate cancer and the utilization of genomic testing in this population, we conducted an analysis of prostate cancer tissue referred for next generation sequencing (NGS) and data interpretation to a Clinical

Laboratory Improvement Amendments (CLIA) certified laboratory. Here, we report the comparative frequency of NGS utilization, the molecular alterations, and potential actionability in prostate cancer.

Results

Frequency of testing

A total of 4864 tissue samples were profiled and interpreted. Table 1 demonstrates that prostate cancer was significantly less frequently profiled than other common malignancies. Indeed, while only 67 patients with prostate cancer underwent NGS, this testing was ordered in 673, 474, and 299 patients, respectively, with lung, breast and colorectal cancer. Amongst genitourinary malignancies, prostate cancer was the least frequently sequenced cancer (bladder cancer was tested in 124 cases, and kidney cancer was sequenced in 121 patients).

Genomic aberrations in prostate cancer

All 67 prostate tumors had at least one genomic aberration (variants of unknown significance (VUS) were excluded). The most common aberrations were in the following genes:

Table 1. Estimated incidence and prevalence of prostate cancer and other malignancies in the United States. Incidence, prevalence, estimated death estimates are based on SEER database (<http://seer.cancer.gov/statfacts>), and five year survival rate for stage IV is obtained from Cancer Research UK (<http://www.cancerresearchuk.org>).

Disease site	Incidence in U.S.	Prevalence in U.S.	5-year survival for Stage IV	Estimated deaths in 2015 in U.S.(%)*	NGS tests performed N (%)**
All Cancers	1,685,210	14,140,254	NA	595,690	4864
Lung	224,200	415,707	2%	158,080 (27%)*	673 (14%)**
Breast	246,660	3,053,450	15%	40,450 (7%)*	474 (10%)**
Colorectal	134,490	1,177,556	5%	49,190 (8%)*	299 (6%)**
Bladder	76,960	587,426	10%	16,390 (3%)*	124 (3%)**
Kidney	62,700	394,336	5%	14,240 (2%)*	121 (2%)**
Prostate	180,890	2,850,139	30%	26,120 (4%)*	67 (1.4%)**

*Refers to percent of deaths from all cancers. Total deaths = 595,690

** Refers to percent of tests done. Total tests done = 4864

Abbreviations: NA = not available

TP53 (55.2% of patients), followed by *PTEN* (29.9%), *MYC* (17.9%), *PIK3CA* (13.4%), *APC* (9.0%), *BRCA2* (9.0%), *CCND1* (9.0%), and *RBI* (9.0%) (Figure 1). A fusion involving *TMPRSS2* was found in 28.4% of patients. The median number of genomic alterations per patient was 3 (range, 1 to 9) (Figure 2A). Fifty-six of 67 patients (84%) had at least one potentially actionable alteration (Table 2). The median number of potentially actionable genes per patient was 2 (range, 0 to 7) (Figure 2B).

Prostate tumors have diverse and unique genomic portfolios

There were 63 distinct genes that harbored alterations; 73% of the altered genes (46 of 63) were found in $\leq 3\%$ of patients; altogether there were 148 distinct alterations. Figure 3 shows that the molecular alterations in each patient were unique. Five patients had the same genomic portfolio: two with only *TP53* alterations, and three with *TP53* and *TMPRSS2* fusions. However, in each case, the precise loci altered within the genes was different. Therefore, at the molecular level, no two patients had an identical molecular portrait.

Diverse pathways are altered in prostate cancer

Signals altered in prostate cancer affected the PI3K/Akt/mTor axis, and the Wnt, DNA repair, cell cycle, and MAPK pathways (Table 2).

PI3K pathway

The PI3K pathway regulates cell proliferation, apoptosis, growth, and longevity and is frequently altered in many malignancies¹⁰ In prostate cancer, the PI3K pathway aberrations (including alterations in *PTEN*, *PIK3CA*, *PIK3R1*, *NF2*, *AKT1*, and *NF1* genes) were found in 37 of 67 patients (52.2%) with metastatic prostate cancer in our dataset. Amongst patients with PI3K axis alterations, *PTEN* was the most frequently altered gene (29.9% of patients (20/67)), followed by *PIK3CA* (13.4%), *PIK3R1* (6.0%), *NF2* (3.0%), *AKT1* (1.5%), and *NF1* (1.5%). Among *PTEN* aberrations, loss of *PTEN* was more frequent (17.9% (12/67)) compared to mutations (11.9%). Amplification was seen in a subset of *PIK3CA*-altered tumors (1.5% of 67 patients).

Wnt pathway

Genomic alterations of the Wnt pathway were previously reported in 18% of metastatic castrate-resistant prostate cancer¹¹ In our study, the frequency of Wnt pathway alterations was 13.5%. Recurrent alterations in *APC* were found in 9.0% of our patient population while mutations in *CTNNB1* occurred in 4.5% of our patients.

DNA repair pathway

In our series, the DNA repair pathway was aberrant in 17.9% of patients. *BRCA2* was the most frequently altered (9.0% of individuals). *ATM* is known to be recruited and activated by DNA double strand breaks, and was altered in 3.0% of our patients. *BRCA1* was less frequently mutated (1.5% of patients). Interestingly, the genes that regulate microsatellite instability, such as *MSH6* and *MSH2*, were mutated in our study in a small subset of individuals (3.0% and 1.5%, respectively).

Cell cycle pathway

The loss of *RBI* is a common event in prostate cancer, and 9.0% of patients were found to harbor an aberration in *RB*. Other genes that regulate the cell cycle also demonstrated alterations: *CCND1* (9.0% of patients), *CDKN2A* (6.0%), *CDK4* (3.0%), *CDKN1B* (1.5%), *CDKN2B* (3.0%), *CCND3* (1.5%), *CDK8* (1.5%), and *CDKN2C* (1.5%). These results imply the important involvement of cell cycle regulators in prostate cancer.

MAPK pathway

The MAPK pathway plays a significant role in oncogenesis and alterations in this pathway are found in many malignancies¹² In total, 14.9% patients with prostate cancer had aberrations in the MAPK pathway. *BRAF* was the most commonly altered gene (6.0% of patients), followed by *KRAS* (4.5%), *HRAS* (3.0%), and *RAF1* (3.0%).

Other potentially actionable targets (Figure 1, Table 2)

In addition to the pathways described above, there were other potentially targetable alterations in very small subgroups. For example, ErbB2 can be targeted by Her2-directed therapy, such as trastuzumab, and was amplified in one of our patients

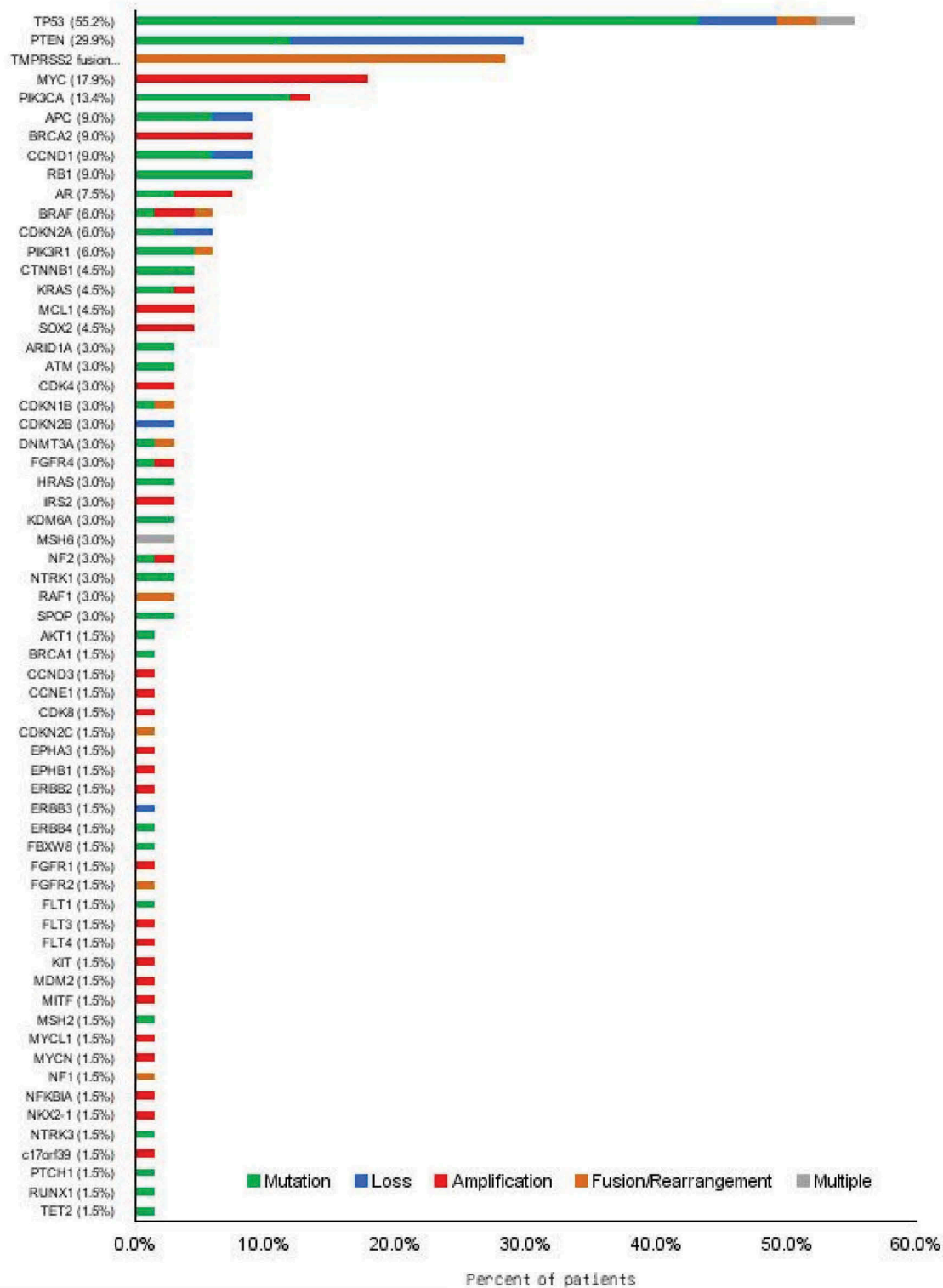


Figure 1. Genomic aberrations in prostate cancer. Next-generation sequencing was performed in 67 prostate cancer patient specimens. Bar represents the frequency of genetic alterations among 67 patients.

(1.5% of the dataset). Other receptor tyrosine kinases, such as *ERBB3*, *ERBB4*, *FGFR1*, *FGFR2*, *FGFR3*, *FLT3*, *KIT*, *NTRK1*, *NTRK3*, were also abnormal, albeit often in only one patient. Although the frequency of each alteration was low, the cumulative frequency was significant—22.4% of patients had at least one such rare, but possibly druggable abnormality.

Biomarker driven clinical trials for prostate cancer

We searched clinicaltrials.gov for all recruiting prostate cancer clinical trials noted during a one year period (starting January 1, 2017). Overall, 208 interventional protocols, of which 162 were therapeutic, were listed. Only 17 (10%) used a non-hormone biomarker for patient selection.

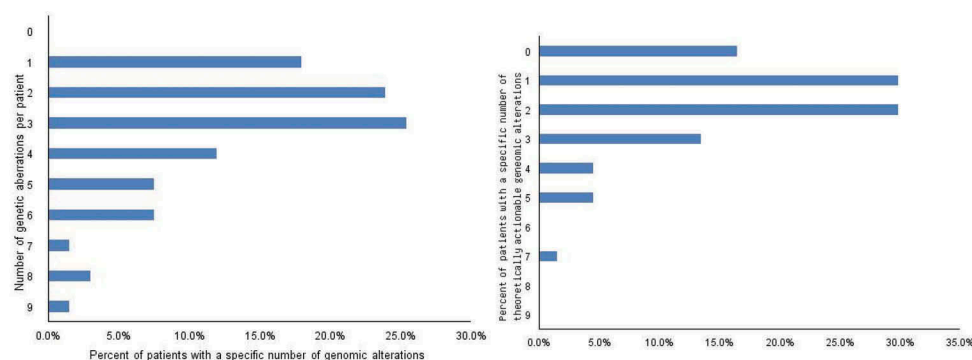


Figure 2. The frequency of genomic alterations per patient and the frequency of actionable genetic aberrations per patient. **A.** The frequency of genetic alterations per patient. **B.** Frequency of theoretically actionable genetic alterations per patient.

Discussion

Analysis of genomic alterations is now clinically feasible, and many guidelines have begun to incorporate NGS analysis into clinical practice.¹³ Further, the FDA recently approved some NGS testing, such as the type utilized in the current study. Our analysis found that NGS was performed infrequently in prostate cancer. Comparatively, NGS was done in prostate cancer at only one tenth of the rate in lung cancer and one sixth of that in breast cancer (Table 1). This low rate of testing is striking because of the high incidence and prevalence of prostate cancer, but might be in part attributable to its more indolent nature. Relatedly, from a historic perspective, very few therapeutic clinical trials in prostate cancer used a non-hormone biomarker for patient selection (only 2% of the 357 therapeutic trials on clinicaltrials.gov in the three year period from September 2011 and September 2014, while 20% of trials included a targeted (non-hormone modulator) agent²). Our current analysis shows that only 10% of recruiting prostate cancer-directed therapeutic trials in 2017 used a non-hormone biomarker for selection of patients. Importantly, previous meta-analyses have demonstrated that deploying targeted agents without a biomarker is associated with exceedingly low median response rates (about 5%) and, furthermore, that overall response rates for therapeutic clinical trials that lack biomarkers is approximately 10% (regardless of the type of agent). In contrast, median response rates in clinical trials enrolling biomarker-selected patient populations for treatment with targeted agents are about 30%.^{14–16}

Our analysis of genomic alterations in prostate cancer confirmed that *TP53* is the most frequently altered gene, followed by the PI3K pathway-associated genes^{11,17} (Table 3). Our study and that of Robinson and colleague¹¹ examined samples from late-stage disease and found *TP53* alterations in 55.2% and 53.3% of patients, respectively, whereas TCGA analysis¹⁷ was conducted using early-stage samples, perhaps explaining why TCGA found *TP53* alterations in only 7.5% of biopsies. The frequency of *TMPRSS2*-fusions in our study was lower than in other studies, perhaps due to small sample size.

Alterations in the PI3K/Akt/mTor pathway occurred in about half of the patients, with the most frequent abnormalities in *PTEN* and in *PIK3CA* genes. Templeton et al. reported that everolimus, an mTOR inhibitor, resulted in a prostate

specific antigen (PSA) response in 11% of patients with castrate-resistance prostate cancer (CRPC), albeit in a non-biomarker-selected population.¹⁸ The PSA response correlated with *PTEN* deletion status, suggesting a biological rationale to target genetic aberrations in the PI3K pathway.¹⁸ However, other studies have suggested that single-agent mTOR inhibitors have low rates of activity in advanced cancers, even in the presence of PI3K/Akt/mTor axis alteration,^{19–21} while combination therapy that includes these agents have significantly better activity in the presence of these aberrations.²⁰

Recent clinical trials demonstrated that DNA-repair pathway aberrations can be a new treatment target. A phase 2 study of the PARP inhibitor olaparib in patients with CRPC harboring DNA-repair pathway abnormalities, including *BRCA2* mutation, demonstrated remarkably high response rates of 88 % in patients with CRPC.²² In our analysis and in Robinson's data¹¹ (Table 3), *BRCA2* was abnormal in 9% to 13% of patients with late-stage disease.

BRAF anomalies were identified in 6% of our study population. Anti-BRAF therapy is a standard of care in melanoma, and can be effective in multiple (but not all) *BRAF*-mutated cancers.^{23,24} The utility of BRAF inhibition is unknown in prostate cancer.

Systematic treatment for prostate cancer has been focused on the androgen pathway, with nine androgen antagonists approved by the FDA for this malignancy. However, our data suggest that there are multiple other alterations that merit exploration in prostate cancer. Some of these alterations may be uncommon, but highly sensitive to targeted agents.^{25,26} For example, some tumors harboring *NTRK* fusions respond well to larotrectinib.²⁵

There are several limitations to the current study. They include the relatively small number of patients studied and the fact that full genomic sequencing was not performed. However, part of the purpose of the study was to understand the utilization of clinical-grade NGS (rather than research-grade NGS such as that in TCGA) in the practice setting. In addition, the data was de-identified, so it is not known whether or not the ordering physicians exploited the NGS results to decide on treatment.

In conclusion, our results demonstrate that patients with advanced prostate cancer have diverse genomic alterations, many of which may be pharmacologically tractable. Important

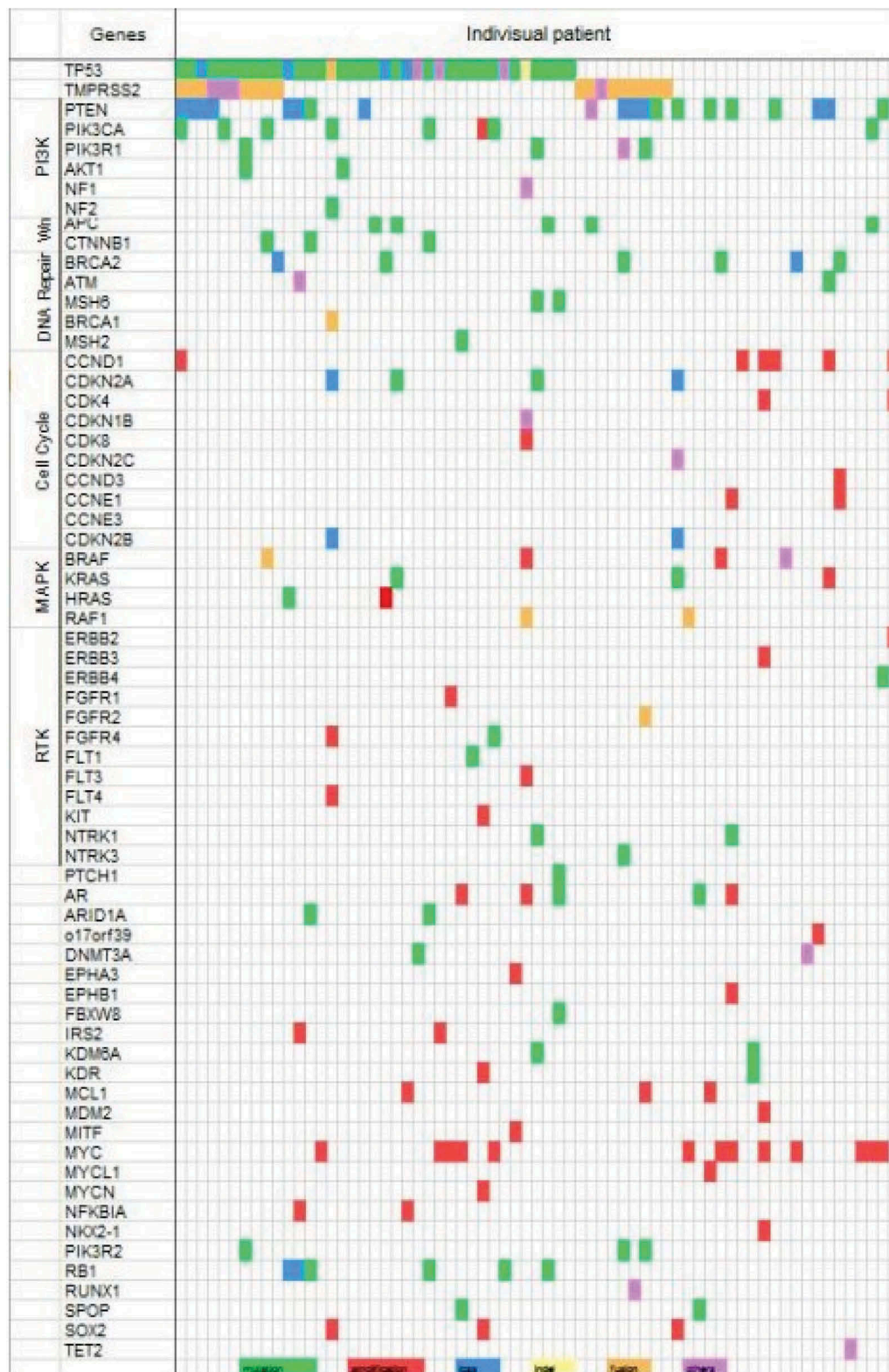


Figure 3. Visualization of genomic alteration patterns in individual patient. Each color represents genomic alterations in each patient. (Green: mutation, Red: amplification, Blue: loss, Orange: fusion, Purple: structural change, Yellow: indel).

pathways impacted include PI3k/Akt/mTor, MAPK, cell cycle, DNA repair and WNT. In addition, small numbers of patients harbor tumors with *ERBB2*, *BRAF* and *NTRK* alterations, all of which are highly druggable in several other malignancies. *ERBB3*, *ERBB4*, *FGFR1*, *FGFR2*, *FGFR3*, *FLT3*, *KIT* aberrations were also

found in some patients and could also be tractable. Even so, there is a disproportionately low rate of genomic testing compared to other common malignancies. Further, there is a paucity of trials that match targeted agents with genomic alterations in prostate cancer, with only about 10% of current prostate cancer trials listed

Table 2. Potentially actionable alterations and examples of targeted agents. The data of 50% inhibitory concentrations (IC50s) is available at <http://tanlab.ucdenver.edu>.

Gene alteration	Frequency	Examples of therapies	Comments	Examples of References/ protocols
PI3K axis (52.2%)*				
PTEN	20/67 (29.9%)	Everolimus	Everolimus demonstrated PSA response in 11% of non-biomarker selected prostate cancer patients.	20
PIK3CA	9/67 (13.4%)	Sirolimus		
PIK3R1	4/67 (6.0%)	Sirolimus		
NF2	2/67 (3.0%)	Sirolimus		
AKT1	1/67 (1.5%)	Sirolimus		
NF1	1/67 (1.5%)	Sirolimus		
WNT pathway (13.5%)*				
APC	6/67 (9.0%)	Sulindac	Sulindac decreased CTNNB1 expression <i>in vivo</i> .	
CTNNB1	3/67 (4.5%)	Celecoxib		
DNA Repair pathway (17.9%)*				
BRCA2	6/67 (9.0%)	Olaparib (<i>ATM</i> , <i>BRCA</i>)	Phase 3 study of olaparib demonstrated responses in 88% of DNA-repair pathway aberrant prostate cancer	NCT01682772 NCT02677038
ATM	2/67 (3.0%)	Cisplatin (<i>BRCA</i>)		
MSH6	2/67 (3.0%)	Carboplatin(<i>BRCA</i>)		
BRCA1	1/67 (1.5%)	Nivolumab, pembrolizumab, or atezolizumab		
MSH2	1/67 (1.5%)	(mismatch repair gene defects (<i>MSH6</i> or <i>MSH2</i>))		
Cell cycle pathway (19.4%)*				
CCND1	6/67 (9.0%)	Palbociclib	Phase 2 trial of palbociclib is in progress in biomarker-selected population.	NCT02905318
CDKN2A	6/67 (9.0%)	Palbociclib		
CDK4	2/67 (3.0%)	Palbociclib		
CDKN1B	1/67 (1.5%)	Palbociclib		
CDK8	1/67 (1.5%)	Palbociclib		
CDKN2C	1/67 (1.5%)	Palbociclib		
MAPK pathway (14.9%)*				
BRAF	4/67 (6.0%)	Vemurafenib Dabrafenib Trametinib Cobimetinib	A study with vemurafenib is in progress in biomarker-selected prostate cancer population.	NCT02208583
KRAS	3/67 (4.5%)	Trametinib Cobimetinib		
HRAS	2/67 (3.0%)	Trametinib Cobimetinib	Phase 2 study with trametinib is planned in CRPC patients.	NCT02881242
RAF1	2/67 (3.0%)	Trametinib Cobimetinib		
Other actionable targets (22.4%)*				
ERBB2	1/67 (1.5%)	Trastuzumab Lapatinib	Pertuzumab interferes with dimerization between <i>ERBB2</i> and <i>ERBB3</i> Lenvatinib inhibits activity of FGFR	26
ERBB3	1/67 (1.5%)	Pertuzumab		
ERBB4	1/67 (1.5%)	Afatinib		
FGFR1	1/67 (1.5%)	Lenvatinib		
FGFR2	1/67 (1.5%)	Lenvatinib		
FGFR4	2/67 (3.0%)	Lenvatinib		
FLT1	1/67 (1.5%)	Lenvatinib		25 NCT02576431
FLT3	1/67 (1.5%)	Lenvatinib		
FLT4	1/67 (1.5%)	Lenvatinib		
KIT	1/67 (1.5%)	Imatinib		
NTRK1	2/67 (3.0%)	Crizotinib		
NTRK3	1/67 (1.5%)	LOXO-101		
PTCH1	1/67 (1.5%)	Vismodegib Sonidegib		

*Some patients had more than one alteration in a pathway; they were counted only once

Abbreviations: CRPC = castrate-resistant prostate cancer; PSA = prostate specific antigen.

on clinicaltrials.gov using a non-hormone biomarker before intervention. Of interest, most of our patients had multiple genomic alterations, which differed from patient to patient. In total, there were 148 distinct abnormalities involving 63 different genes. Similar phenomena have been seen in other tumor types as well, and suggest that individualized combinations of cognate targeted drugs may be necessary to optimize treatment²⁷⁻²⁹ Finally, three patients (4.5%) had an abnormal mismatch repair gene, which has been associated with high tumor mutation burden and response to checkpoint inhibitor immunotherapy in many tumors^{30,31} Taken together, these data indicate that more genomically based studies in prostate cancer are urgently needed.

Table 3. Comparison of genomic alteration frequencies across different genomic profiling studies in prostate cancer.

	Current report N = 67 patients	Robinson et al ¹¹ N = 150 patients	TCGA N = 333 patients ¹⁷
Stage	Late stage	Late stage	Early stage
<i>TP53</i>	55.2%	53.3%	7.5%
<i>PTEN</i>	29.9%	40.7%	45.7%
<i>TMPRSS2</i> translocation	28.4%	56.7%	45.7%
<i>MYC</i>	17.9%	14%	7.5%
<i>PIK3CA</i>	13.4%	5.3%	4.8%
<i>APC</i>	9.0%	8.7%	5.4%
<i>BRCA2</i>	9.0%	13.3%	3.3%
<i>BRAF</i>	6.0%	2.7%	3.9%

Patients and methods

Patients

We analyzed prostate cancer specimen data submitted to Foundation Medicine Inc. (Cambridge, MA) (<https://www.foundationmedicine.com/>) for genomic sequencing and to N-of-One Inc. for data interpretation. The diagnosis and the origin of tissue were provided by ordering physicians from multiple institutions. The prostate cancer data was derived from a database of 4864 consecutive Foundation Medicine samples annotated by N-of-One starting in December 2011. The study was conducted in accordance with University of California San Diego Institutional Review Board guidelines for a de-identified database.

Tissue preparation, genomic sequencing, and bioinformatic analysis

Samples from formalin-fixed paraffin-embedded tissue were submitted to a CLIA-certified lab for genomic sequencing (Foundation Medicine). The details of sample requirement, DNA extraction and NGS were described previously; most samples represent advanced disease³² Targeted exons of 182 or 236 cancer-related genes and introns of 14 or 19 genes frequently rearranged in cancer were sequenced (Supplemental Table 1A and 1B) (Overall, 2974 cases were sequenced on the 182 gene panel and 1890 cases on the 236 gene panel.)

Average depth of sequencing was greater than 250x, with 100x at > 99% of exons. This method of sequencing enabled to detect copy number changes, gene rearrangement, and single nucleotide variants with 99% specificity and 99% sensitivity for base substitution, and 95% sensitivity for copy number changes. Amplification was defined as copy number increase of ≥ 8 copies (equivocal, 6 to 7 copies). Sequencing data was analyzed with a customized analysis pipeline described previously³² Clinical interpretation of genetic alterations were provided by N-of-One (<https://n-of-one.com>)

Disclosure of potential conflict-of-interest

Razelle Kurzrock receives research funding from Genentech, Incyte, Merck, Serono, Pfizer, Sequenom, Foundation Medicine, and Guardant, as well as consultant fees from Loxo, X Biotech, and Actuate Therapeutics, speaker fees from Roche, and an ownership interest in Curematch Inc. Sheryl Elkin, Brett Tomson, and Jennifer Carter are employees of N-of-One, Inc. Sadakatsu Ikeda has nothing to disclose.

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Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and material

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Authors contributions

SI, SKE, JLC, and RK designed the study. SI and SKE analyzed the data to generate the results, created the figures and tables. SI and SKE drafted the manuscript. All authors edited and approved the final manuscript.

List of abbreviations

NA = not available

CRPC = castrate-resistant prostate cancer

PSA = prostate specific antigen.

ORCID

Sheryl K. Elkin  <http://orcid.org/0000-0002-2283-3842>

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